



"... the fact that the compound crystallizes in three distinct crystalline forms, an instance of polymorphism, does not render the compound in these crystalline forms patentable over the compound itself..."; and

"... it is generally known in the chemical arts that many compounds crystallize in two or more distinct forms, morphologies..."

The rejection is based in part on the disclosure of Kirk-Othmer, which teaches that a chemical compound can exist in crystals of very different size and form. Kirk-Othmer also teaches that it is possible in many cases to influence form and size of the crystals by a different technology of the crystallization, for example by application of additives. The author presents an overview of different characteristics of crystals such as size, habit, polymorphic forms and agglomerates. The focus of the representation is the change of the habit by the use of additives (habit modifiers). The reader of this article might conclude that size, habit, polymorphism or agglomerate represent appearances of the same order. However, this is incorrect.

Between habit (needlelike, long prismatic, cubic and so on) and modification (polymorphic crystal for) a fundamental difference exists. The polymorphism of  $\text{NH}_4\text{NO}_3$ , discussed in Kirk-Othmer, can be used as an example. In the American data base Powder Diffraction File (PDF), a collection of the X-ray powder data of about 100,000 substances (Powder Diffraction File. International Center for Diffraction Data. Newton Square, Pennsylvania, Sets 1-47 (1997), the following statements are contained for forms II and III:

PDF-pattern 47-865, Ammonium Nitrate, Form II

Temperature (during the recording of the X-ray diffractogram): 90°C

Formula:  $\text{NH}_4\text{NO}_3$

Number of formula units in the elementary cell:  $Z = 2$

Symbol of the space Group: P4bm

Number of the space Group: 100

Lattice constants:

$$a = 5.70600$$

$$b = 5.70600$$

$$c = 4.91600$$

$$\alpha = \beta = \gamma = 90^\circ.$$

From P4bm follows:

- tetragonal crystal system
- ditetragonal-pyramidal crystal class, symbol: 4mm
- primitive tetragonal Bravais lattice.

In Kirk-Othmer a trigonal modification was postulated above 84.2°C. This does not correspond with the newest results.

In the crystal structure of form II are put into one another several primitive tetragonal lattices, in which case their corner points are occupied by H, N or O. This structure type must correspond to the possible point positions in the space-group P4bm (International Tables for Crystallography. Birmingham, Kynoch Press) and is different from all other crystals. This crystal as a singular crystal type is defined by a name, like a plant (in the biological system), a chemical compound (in the chemical system) or a mineral.

The specific X-ray diffraction diagram (the d-values of pattern 47-865), is like an image of the structure (Fourier transformation), an unambiguous criterion of this crystal type.

As a consequence of this structure, form II can exist only in the following seven crystal forms as well as their combinations (crystal class 4 mm): ditetragonal pyramids {hkl}, ditetragonal prisms {hk0}, tetragonal pyramids {h0l}, tetragonal prisms {100} and {110}, pedia {001} and {00-1}.

PDF-pattern 47-866, Ammonium Nitrate, Form III

Temperature (during the recording of the X-ray diffractogram): 48.5°C

Formula:  $\text{NH}_4\text{NO}_3$

Number of formula units in the elementary cell:  $Z=4$

Symbol of the space Group: 62

Lattice constants:

$a = 7.158$

$b = 7.7100$

$c = 5.83700$

From Pbnm follows:

-orthorhombic crystal system

-rhomby-dipyramidal crystal-class, symbol mmm,

-primitive rhombic Bravais lattice

In the crystal structure of form II are put into one another several primitive orthorhombic lattices, in which case their corner points are occupied by H, N or O. This structure type must correspond to the possible point positions in the space group Pbnm (International Tables for Crystallography. Birmingham, Kynoch Press) and is different from all other crystals. The specific X-ray

diffraction diagram (the d-values of pattern 47-866), is like an image of the structure (Fourier transformation), an unambiguous criterion of this crystal type.

As a consequence of this structure, form II can exist only in the following seven crystal forms as well as their combinations (crystal class mmm): rhombic dipyramids  $\{hkl\}$ , rhombic prisms  $\{hk0\}$ ,  $\{h0l\}$  and  $\{0kl\}$ , pinakoids  $\{100\}$ ,  $\{010\}$  and  $\{001\}$ .

#### Polymorphism

Both structures have a defined stability domain. Below 84.2°C, form III and above 84.2°C, form II has the lower vapor pressure. Therefore, the phase transition (form III  $\rightarrow$  form II) takes place at 84.2°C.

#### Habit Modification

Assuming, for example, a combination of a long ditetragonal prism and the two pedia would be the normal (most frequent) crystal form of form II, the habit would be long prismatic. This form could be theoretically avoided by crystallization with additives to obtain, for example a combination of the prism  $\{110\}$  and the two pedia, the prism nearly as long as the side of the pedion. The habit would then be cubic. However, this would not result in a crystal belonging to the cubic crystal system, as the Bravais lattice would still be tetragonal. The proportion  $a/c$  in the elemental cell would still be 5.706/4.916. The cubic crystal would still be a combination of crystal forms belonging to the seven possible forms in the crystal class 4mm. This results because only the growth rate in distinct lattice directions has been changed, and not the crystal structure itself.

It is also at least theoretically possible to make in this way crystals of form II which look like crystals of form II. However, the lattice will always remain orthorhombic.

#### Mineralogy

In mineralogy, polymorphic crystals generally have true names. Diamond and graphite are two modifications of carbon. Quartz, tridymite, cristobalite, coesite, and stishovite are modifications of  $\text{SiO}_2$ . Calcite and aragonite are two modifications of  $\text{CaCO}_3$ .

In the case of crystal modifications, there is a very sharp "kind" criterion which is the crystal structure (including Bravais lattice, atom positions in the elemental cell, possible crystal forms, etc. ) Furthermore, the structure can be identified by X-ray diffraction, as recited for presently claimed modifications A, B and C in the claims. The Examiner has stated that "the instant crystalline morphologies would have been obvious to one of ordinary skill in the art." Applicants respectfully disagree. Quartz was described for the first time by Agricola (1529), tridymite by Rath (1868), cristobalite by Rath (1887), coesite by Sosman (1954), stishovite by Chao, Fahey, Littler & Milton (1962), yet all of these forms are represented by the chemical structure  $\text{SiO}_2$ . The structure of the monoclinic form of the drug carbamazepine was solved in 1991 by Himes, but the trigonal form of carbamazepine was not described until 1987 by Lowes et al. Up until now, it has not been possible to answer the question of whether there are more  $\text{SiO}_2$  or carbamazepine (or Retigabine) modifications. Attempts to calculate the possible crystal structures of a chemical compound have been successful only in a few special cases.

There may exist one or several modifications of one element or compound. However, there do not exist an endless number of modifications, because modifications correspond to arrangements of molecules with minimal free energy versus temperature and pressure. This results in ranges of stability for the different modifications.

In summary, Applicants respectfully submit that modifications of polymorphic substances in general, and of Retigabine in particular are patentable, because

1. Different crystal modifications represent different crystal species;
2. Often several, but not an endless number of modifications exist;
3. Unambiguous methods for determination of their identities exist (e.g. X-ray diffractogram); and
4. At present, no general method is available to predict the existence or nonexistence of crystal modifications.

Furthermore, it is noted that a number of U.S. patents covering such crystal modifications have issued, for example U.S. 4,521,431 and U.S. 5,021,582, copies of which are attached for the Examiner's convenience.

Different modifications of the chemical compounds of formula I were not known prior to the work leading to the present application. The three modifications of compound I that are the subject matter of the present application are not inherent in the prior art.

Crystallizates were not obtained until 1994 during the transfer of the chemical method developed for the production of compound I, which is described in U.S. 5,384,330, from the laboratory into production, which crystallizates differ significantly according to the form and size of the crystals,

and which resulted in problems in the reproducible production of physically and physicochemically homogeneous products.

It was the investigation of these different crystallizates, e.g. with X-ray diffraction methods, which led to the discovery of three modifications which were unambiguously identified in particular by their characteristic X-ray diffractograms (see Fig. 1 of the present specification). The coincidence-free X-ray reflexes (Bragg angles in  $2\theta$  and  $d$  values in Å) are also indicated at pages 3 and 4 of the specification.

There are also different arrangements of the molecules of the compound of formula I, determined by X-ray photographic methods, in the elementary cells of the crystals of modifications A, B and C. These studies also show that A, B and C are very different.

Modification A crystallizes in the monoclinic space group  $P2_1/n$ .

Modification B crystallizes in the monoclinic space group  $C2/c$ .

Modification C crystallizes in the orthorhombic space group  $Pbca$ .

It was the discovery and identification of three modifications of compound I and the detailed investigation of their different physical and physico-chemical properties which made possible the development of methods for its isolation and the justification of possibilities of use for the production of special pharmaceutical formulations which are based on the particular special properties (physico-chemical stability range, crystal form, crystal size) of the individual modifications.

Modification A is stable below  $80^\circ\text{C}$ , even at elevated temperatures and air humidities, and exhibits no change in the crystalline structure upon contact with various solvents, especially also upon contact with water. This is

advantageous in the production and storage of pharmaceutical forms of medicine under extreme conditions, e.g., in a tropical climate. Modification A has a granular nature of the powder which is favorable for the production of certain pharmaceutical formulations, e.g., for the production of tablets, on account of the preferred isometric shape of the crystals.

Modifications B and C are stable up to high temperatures (142 and 130°C, respectively) and can therefore be used in galenic processes requiring the use of high temperatures (e.g. in fusion granulation).

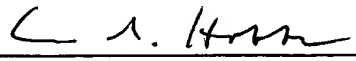
Modification C, which can be produced in fine, crystalline form, can be used with advantage for the production of dry ampoules on account of its better solubility.

For all of the above reasons, withdrawal of the 35 USC § 103 rejection is respectfully requested.

All objections and rejections having been addressed, the application is believed to be in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

PILLSBURY MADISON & SUTRO

By   
Ann S. Hobbs, Ph.D.  
Registration No. 36,830  
Tel. No.: (202) 861-3063  
Fax No.: (202) 822-0944

1100 New York Avenue, N.W.  
Ninth Floor  
Washington, D.C. 20005  
(202) 861-3000